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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 23

mailed out date 9/18/11

Application Number: 08/520,946
Filing Date: August 30, 1995
Appellant(s): Brow et al.

Virginia S. Medlen of Medlen & Carroll, LLP
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed May 27, 1999.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

This appeal involves claims 1, 3-29 and 31-54.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The amendment after final rejection filed on November 6, 1998 has been entered.

Claims 1, 5-10, 19 and 44 have been amended subsequent to the final rejection. The amendment to the claims has been entered after the filing of the appeal brief. The amendment does not change or alter the rejection of the claims under 35 USC 103(a) as set forth in the previous rejection made at the time of the Final rejection, which was repeated at the time of the Advisory Action, Paper No. 18, mailed November 23, 1998.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because there is no argument provided for claims 1 and 44. Claim 44 is distinguished over claim 1, only in the limitation that Manganese is present in the reaction. The open language of claim 1 embraces the limitation of manganese in the reaction, and therefore, claim 44 is a subset of claim 1 and the claims should be grouped together.

(8) Claims Appealed

The copy of the appealed claims contained in Appendix A and Appendix B to the brief is correct. A copy of the amended claims entered by this Examiner's Answer, claims 1, 5-10, 19 and 44 are contained in Appendix B.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

1) US Pat. No. 5,422,242 Young 6-6-95

2) Lyamichev et al. Structure-specific endonucleolytic cleavage of nucleic acids by eubacterial DNA polymerases. Science. Vol. 260:778-783. 5-7-1993.

3) Seela and Rolling. 7-deazapurine containing DNA: efficiency of 7-deaza-dATP, and 7 deaza-dITP incorporation during PCR-amplification and protection from endodeoxyribonuclease hydrolysis. Nuc. Acids Res. Vol. 201(1):55-61. 5-1992.

4) Young et al. Detection of hepatitis C virus RNA by a combined reverse transcription-polymerase chain reaction assay. J. Clin. Microbiol. Vol. 34(4):882-886. 4-1993.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 3-29 and 31-54 are rejected under 35 U.S.C. 103(a). This rejection is set forth in prior Final Office action, Paper No. 15, mailed August 31, 1998, repeated below:

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3-29 and 31-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyamichev et al. in view of Young, Seela and Roling, and Young et al.

The claims are drawn to a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera

Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus (HCV) and simian immunodeficiency virus (SIV). The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is treated to form (secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquaticus* DNA polymerase, *Thermus thermophilus* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus

gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et al. (see entire reference) taught a method for cleaving an isolated nucleic acid where the nucleic acid was treated to form (secondary) cleavage structures. The cleavage structures were cleaved with a cleavage means. The cleavage means was an enzyme, which was a nuclease, which was selected from the group consisting of *Thermos aquatics* (Tac) DNA polymerase and *Thermos thermophilous* (Tth) DNA polymerase. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of reference nucleic acid structures. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus. Lyamichev et. al. taught that this method can be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid.

Lyamichev et al. did not teach a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein

the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Lyamichev et. al. also did not teach that the microorganism may be a virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The reference did not teach that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. Lyamichev et al. did not teach that the nucleic acid may comprise a nucleotide analog, where the nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The reference did not teach that the PCR may be done with these nucleotide analogs or that the PCR primers were from ribosomal RNA, which may be 16S ribosomal RNA.

Young (see especially columns 3-4 and 10) taught the use of PCR with the nuclease *Thermos aquaticus* (Tac) DNA polymerase to identify the polymorphic loci of ribosomal 16S RNA from *Mycobacterium spp.* which increased the speed, accuracy and sensitivity of detection of disease causing microorganisms which were difficult to culture and could take up to several weeks to identify by culture methods.

Seela and Roling (see especially pages 55 and 61) taught the use of 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions.

Young et al. (see especially the introduction) taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics, which was an effective means of direct detection of HCV that streamlined the procedure, reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

It would have been obvious to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method for identifying strains of microorganisms, which may be bacteria or viruses, where the microorganisms were identified by cleaving the isolated nucleic acid which was treated to form (secondary) cleavage with a nuclease because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. Seela and Roling recited the use of Tac polymerase with nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions and taught that the use of these nucleotide analogs would have helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Young et. al. taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics. They taught that the use of Tth DNA polymerase in PCR was an effective means of direct detection of HCV which streamlined the procedure and reduced potential contamination of

the reaction by eliminating the addition of a second enzyme and increasing the specificity of the primer extension.

One of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev et al. with Young, Seela and Roling, and Young et al. to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. Lyamichev et al. also taught that the polymerase was a single stranded endonuclease which recognized hairpin structures. Seela and Roling taught the method using Tth DNA polymerase or Tac DNA polymerase which incorporated nucleotide analogs 7-deaza-dATP, 7-deaza-dGTP and dUTP in PCR reactions demonstrating that the use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems which are frequently encountered in polymerase reactions. Also, the use of nuclease *Thermos thermophilous* DNA polymerase in PCR assays was an effective means of direct detection of HCV as taught by Young et al. because it streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme which also increased the specificity of the primer extension. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Lyamichev et al., Young, Seela and Roling, and Young et al.

(11) Response to Argument

The arguments are set forth in the appeal brief which are not discussed in the rejection set forth in Paper No. 15. They do not change the rejection in any way, and are as follows:

3. Appellant's arguments filed in Paper No. 14, filed June 22, 1998 and Paper No. 17, filed November 6, 1998 have also been fully considered but they are not persuasive as set forth in the response below.

1) In response to appellant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the Lyamichev et al. reference taught the limitations of enzymatic cleavage by an enzyme which cleaves a single or double stranded nucleic acid substrate where the substrate may form a secondary structure which is as a cleavage site recognized by the enzyme. The teachings of Lyamichev et al. recite the use of PCR throughout the reference. The teachings of Young, Seela and Roling, and Young et al. demonstrate modifications to PCR to improve the technique. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Lyamichev et al. with those of Young, Seela and Roling and Young et al. to improve the PCR technique which they were all practicing.

2) In response to appellant's argument that the references fail to show certain features of appellant's invention, it is noted that the features upon which appellant relies (i.e., "the 5' nuclease activity of DNA polymerases may be used to characterize sequence variation between nucleic acids by cleavage of intra-strand secondary structure") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

3) At page 17 of the Appeal Brief, lines 1-9, appellants put forth an argument that Lyamichev et al. taught **allele specific PCR** (emphasis added), and that there was no motivation to combine the **allele specific PCR** of Lyamichev et al. with the **PCR** of Young, Seela and Rolling, or Young et al. No attempt is made in the rejection of the claims to discriminate between **allele specific PCR** and **PCR**. The **PCR** of **allele specific PCR** is not patentably distinct from the **PCR** taught by Young, Seela and Rolling, or Young et al. Therefore, the argument is moot.

4) At page 18 of the Appeal Brief, lines 3-15, Appellants argue that Lyamichev et al. teach away from the instant claimed invention refers to the issue of primer directed cleavage of the nucleic acid, it is noted that the features upon which appellant relies (i.e., lack of primers) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re*

Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Therefore, the argument is moot. This point is discussed further in item "6)" below.

5) Appellants have argued at page 19 of the Appeal Brief, lines 3-13, that the prior art, as recited in Barr et al. (see appendix "C" of the Appeal Brief) "taught away" from the instant invention, asserting that the use of "nucleotide analogs...prevents higher secondary structures [abstract]". Contrary to this assertion, Barr et al. (see page 428, column 3, last two sentences) state "7-deazaguanine, by virtue of replacement of N-7 of the guanine ring by the methine moiety, precludes Hoogstgeen bond formation (21). In contrast to inosine, however, Watson-Crick base pairing through the exocyclic amino group at the 2 position of the heterocycle is not impaired (21)." This statement in Barr et al. clearly sets forth the ability of nucleotide analogs in a single stranded sequence to form secondary structures as recited in the instant claimed invention. This does not "teach away" from the invention. Therefore, the argument is moot.

6) Appellants have argued in Paper No. 14 that the addition of the limitation to the claims that the structure of the nucleic acid substrate form one or more intra-strand secondary structures, where the cleavage means reacts with the intra-strand secondary structures is a distinguishing limitation. Lyamichev et al. taught at page 779, column 1, and at page 781, column 3, that a primer was not required for cleavage, and that the enzyme could recognize and cleave intra-strand secondary structures. It is noted that the declaration of Mary Ann D. Brow, filed November 6, 1998 accurately states that Lyamichev et al. taught that a primer was necessary for

cleavage of RNA. This is not sufficient to distinguish the instant claims over the prior art because the instant claims recite a *nucleic acid*. Amending the claims to limit the invention to RNA may provide a patentable distinction.

7) It has been argued in Paper No. 17 that cleavage specificity and efficiency is improved by the instant claimed invention over the teachings of Lyamichev et al. These limitations are not claimed and may provide patentable distinction over the prior art.

8) Appellants have argued in Paper No. 17 that Young, Seela and Roling and Young et al. do not teach the cleavage of intra-strand secondary structures in nucleic acids. This is true. These references are relied upon here to teach obvious methods which are well known in the art, which have been included as claimed limitations to the base invention which is taught by Lyamichev et al. These teachings are provided to demonstrate that the claimed limitations are merely adaptations of well known methods.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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August 9, 1999